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TITLE: Evaluation of Feasibility for a Case-Control Study of
Pituitary-Ovarian Function in Premenopausal Women with
Breast Cancer

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Background: The association of serum estrogens with breast cancer in premenopausal women has not been clearly established. **Objective/Hypothesis:** Evaluate safety and feasibility of a case-control study that uses gonadotropin releasing hormone (GnRH) stimulation tests to evaluate sensitivity of the hypothalamic pituitary ovarian (H-P-O) axis in premenopausal women with breast cancer compared to unaffected premenopausal women. Hypotheses to be tested in full-scale study: 1) premenopausal women with breast cancer secrete more luteinizing hormone (LH) and follicle stimulating hormone (FSH) in response to GnRH compared to controls; 2) premenopausal women with breast cancer secrete more estradiol and testosterone compared to controls in response to gonadotropins, which is related to their higher insulin like growth factor - 1 (IGF-1) levels; and 3) increased estradiol production by premenopausal women with breast cancer is due to increased enzyme activity at a specific step in steroidogenesis. **Specific Aims:** Specific aims of the feasibility study are: 1) determine feasibility of a full-scale study; 2) gather preliminary data on basal and GnRH stimulated serum gonadotropins, testosterone and estradiol. **Key Research Accomplishments:** 1) phase 1, which included ten healthy controls, was completed; 2) currently recruiting for phase 2, which includes women with a history of breast cancer.

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Introduction: Elevated serum estrogen levels in postmenopausal women have been shown to increase the risk of breast cancer. However, the association of serum estrogens with breast cancer in premenopausal women has not been established. The purpose of this study is to determine the safety and feasibility of conducting a case-control study that uses gonadotropin releasing hormone (GnHR) stimulation tests to evaluate the sensitivity of the hypothalamic pituitary ovarian (H-P-O) axis in premenopausal women with breast cancer compared to unaffected premenopausal women. The full-scale study will determine if: 1) the anterior pituitary of pre-menopausal women with breast cancer secretes more luteinizing hormone (LH) and follicle stimulating hormone (FSH) in response to GnRH compared to controls; 2) the ovaries of pre-menopausal women with breast cancer secrete more estradiol and testosterone in response to gonadotropins, and this is related to their higher insulin like growth factor -1 (IGF-1) levels compared to controls; 3) increased estradiol production by the ovaries in premenopausal women with breast cancer is due to increased enzyme activity at a specific step in steroidogenesis.

Body: Research accomplishments are described for each task outlined in the approved statement of work.

Task 1: Prepare for data collection, Months 1-2

- a. *Finalize data collection protocol and forms.* This activity has been completed and all questionnaires have been approved by both the FCCC IRB and the DOD IRB.
- b. *Finalize database design and data entry screen.* This activity has been completed.
- c. *Hire and train program coordinator.* This activity has been completed.

Task 2. Identify and recruit participants, Months 2-6

- a. *Search the FCCC Tumor Registry and Health Information Management System (HIMS) to identify potential cases and benign breast disease controls.* The FCCC IRB required that we conduct the study in phases – recruiting and conducting GnRH stimulation tests in healthy premenopausal women during the first phase and conducting GnRH stimulation tests in premenopausal women treated for stage 0 or stage 1 breast cancer who did not receive any chemotherapy and who completed adjuvant therapy at least one year earlier during the second phase. Twenty one women who may be potentially eligible for Phase 2 have been identified by using HIMS.
- b. *Obtain physician approval to contact cases and benign breast disease controls.* Twenty women have been sent letters and followed up. Of those, 9 women were unresponsive to the letter and phone calls, 6 were not interested in participating and three were not eligible for the study.
- c. *Identify one friend control who is eligible and agrees to participate for each case.* Friend controls have been replaced with healthy community controls because of the IRB's concerns about asking cases to identify friends who did not have breast cancer. This was approved in the original protocol submitted to the DOD.
- d. *Send approximately 50 letters.* Completed for Phase 1.

- e. *Perform approximately 50 telephone interviews.* Completed for Phase 1. An additional 68 women were interested after recruitment for healthy women ceased. Recruitment began for Phase 2 of the study. Seven women contacted FCCC for information, however none were eligible for the study.

Task 3. Conduct data collection visits, Months 3-8.

- a. *Administer 20 questionnaires.* Ten questionnaires have been administered.
- b. *Measure heights and weights of 20 participants.* Heights and weights have been measured for 10 participants.
- c. *Perform 20 GnRH stimulation tests, collect and store serum specimens.* Ten GnRH stimulation tests have been performed. These serum specimens were collected and are currently stored in the FCCC Biosample Repository.
- d. *Isolate DNA from lymphocytes for 20 participants and store.* DNA has been isolated for 10 participants and is currently stored in the FCCC Biosample Repository.
- e. *Key and verify data.* Data has been keyed and verified for 10 participants.

Task 4. Create a serum pool for laboratory quality control, Month 8. This task will be done when we get closer to conducting laboratory analyses.

Task 5. Measure LH, FSH, estradiol, testosterone, IGF-1, and IGFBP-3 concentrations in serum from 27 participants, Months 9-10. This task will be done after the GnRH stimulation study. Estradiol has been measured in 10 samples. All results were found to be within normal range. Based on these results the FCC Data and Safety Monitoring Board and the DOD IRB approved continuing to Phase 2 of the study, which involves testing women with a history of stage 0 or 1 breast cancer.

Task 6. Analyze data and write reports, Months 11-12. This task will be completed in the future.

- a. Perform statistical analyses
- b. Write final report
- c. Begin writing grant proposal for full scale study

Key Research Accomplishments: The FCCC IRB required that the study be conducted in two phases. The first phase includes 10 healthy premenopausal women. The second phase includes 10 premenopausal women diagnosed with early stage breast cancer and have not had chemotherapy.

- Phase 1 has been completed.
- Recruitment has begun for Phase 2 of the study.

Reportable Outcomes: None at this time.

Conclusions: This is an interim report for a pilot study. Based on our experience to date, it appears that we will be able to recruit healthy controls for a full scale case-control study. It remains unclear whether we will be able to recruit women who have had breast cancer. Identification of the hormonal cause for breast cancer in premenopausal women could ultimately

lead to detection of populations at increased risk, approaches to screening for women at high risk, and/or chemopreventive strategies that target the responsible enzyme or regulatory protein.

References: None at this time.

Appendices: None at this time.